REMARKS

Upon entry of the foregoing amendment, claims 1-9, 11, and 13-34 are pending for the Examiner's consideration, with claims 1, 11, 13, 18, 29, and 33 being the independent claims. Claims 10 and 12 have been previously cancelled without prejudice to or disclaimer of the subject matter contained therein. Independent claims 1, 11, 13, 18, 29, and 33 have been amended herein to recite that the microparticles are suspended in the injection vehicle at a concentration of from about 175 mg/ml to about 400 mg/ml. A conforming amendment to dependent claim 4 has also been made. Applicants submit that the foregoing amendments introduce no new matter. In this regard, the Examiner is referred to, for example, page 19, lines 8-10, page 20, lines 6-8, and page 26, lines 23-28 of the application as originally filed.

Description of the Invention

As explained on page 8 of the application as originally filed, the present invention relates to injectable compositions having improved injectability, and to methods for the preparation of such injectable compositions. The injectable compositions of the present invention overcome injectability problems, particularly injectability failures that occur upon injection into muscle or subcutaneous tissue. Such injectability failures will be referred to herein as "*in vivo* injectability failures." *In vivo* injectability failures often manifest themselves in the form of a plug at the tip of the needle, and occur immediately or shortly after injection has been initiated. *In vivo* injectability failures are typically not predicted by laboratory or other *in vitro* testing.

The inventors have unexpectedly discovered that injectability is improved, and *in vivo* injectability failures significantly and unexpectedly reduced, by ***increasing*** the viscosity of the fluid phase of an injectable suspension. Notably, the inventors have unexpectedly discovered that increasing the viscosity of the fluid phase of the injectable suspension decreased injection failure rate, even when the microparticle concentration was raised to above 175 mg/ml (*see*, for example, pages 19-20 of the application as originally filed). This is in contrast to conventional teachings that an increase in the viscosity hinders injectability and syringeability. As explained on pages 2-3 of the application as originally filed, viscosity is typically kept low, in order to facilitate mixing, resuspension of the particles with the vehicle, and to make the

suspension easier to inject (*i.e.*, low force on the syringe plunger). Conventional parenteral suspensions are dilute, with limitations for viscosity because of syringeability and injectability constraints. *See*, for example, the Floyd, *et al.* Chapter referred to on page 2 of the application as originally filed.

Viscous vehicles, however, are not optimal for preparing homogeneous suspensions of microparticles because of the relative inability of viscous vehicles to penetrate and wet out a mass of dry particles. Suspensions prepared with viscous vehicles are prone to clump irreversibly. Consequently, such suspensions are not injectable via needles of medically acceptable size. A further disadvantage of viscous suspensions is the lack of ease of transferring such suspensions from the vial or container used to prepare the suspension to the syringe used for injection.

The present invention also solves the additional problems that arise from use of a viscous injection vehicle. In accordance with the present invention, microparticles are suspended in an injection vehicle having suitable wetting characteristics. The viscosity of the fluid phase of the injectable suspension is increased prior to injecting the suspension in order to improve injectability, and to reduce *in vivo* injectability failures.

Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-9, 11, 13, and 15-34 under 35 U.S.C. § 103(a) as being unpatentable over WO 97/44039 in view of WO 95/13799. The Examiner has rejected claim 14 under 35 U.S.C. § 103(a) as being unpatentable over WO 97/44039 in view of WO 95/13799 and U.S. Patent No. 5,631,021. Each of independent claims 1, 11, 13, 18, 29, and 33 have been amended herein, thereby rendering these rejections moot.

Without conceding the propriety of the Examiner's rejection in the Final Office Action, and solely to advance the prosecution of the present application, each of independent claims 1, 11, 13, 18, 29, and 33 has been amended herein to recite that the microparticles are suspended in the injection vehicle at a concentration of from about 175 mg/ml to about 400 mg/ml. Applicants respectfully submit that none of the documents cited by the Examiner discloses or suggests the claimed combination of viscosity and microparticle concentration

range. None of the documents cited by the Examiner discloses explicitly or inherently a microparticle concentration range between 175 mg/ml and 400 mg/ml. Moreover, Applicants respectfully submit that the claimed combination of high viscosity and high microparticle concentration is unexpected in light of the conventional teaching (as described, for example, in the Floyd *et al.* Chapter discussed on page 2 of the application) that an increase in viscosity ***and*** an increase in concentration of solids in suspension ***both*** hinder the syringeability of suspensions. As such, one skilled in the art would not expect the increased viscosity and concentration of the microparticles as claimed to provide injectability through a needle of 18-22 gauge, or more generally, through a needle of medically acceptable size. For at least the foregoing reason, Applicants respectfully submit that the rejections under § 103(a) cannot properly be maintained for the claims as presented herein.

Applicants respectfully submit that the rejections under § 103(a) cannot properly be maintained for the additional reason that the documents cannot properly be combined. As fully explained in the Amendment in Response to Non-Final Office Action dated December 5, 2006, there is no motivation to combine WO 97/44039 with WO 95/13799 because WO 97/44039 teaches away from use of risperidone itself, which is the active agent used in WO 95/13799, and there would be no reasonable expectation of success to substitute risperidone encapsulated in a biodegradable and biocompatible polymer for the crystalline form of the metabolite. Importantly, in attempting to explain why Applicants' arguments are not persuasive, the Examiner never directly addresses, much less refutes, the foregoing assertions. Rather, the Examiner merely recites three sentences of what the two documents allegedly teach (*See*, page 6 of the Final Office Action). Contrary to law and U.S. Patent and Trademark Office practice[1], the Examiner provides ***no*** reason why one skilled in the art would combine the teachings of the "Ramstack" (WO 95/13799) and "Francois" (WO 97/44039) documents. For at least this reason, Applicants respectfully submit that the § 103(a) rejections were not properly made in the Final Office Action, and nor can they properly be maintained against the claims as presented herein.

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[1] The Memorandum dated May 3, 2007 from Margaret A. Focarino, Deputy Commissioner for Patent Operations, regarding the Supreme Court decision in *KSR Int'l Co. v. Teleflex, Inc.*, states that "in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." This the Examiner has not done, and cannot do.

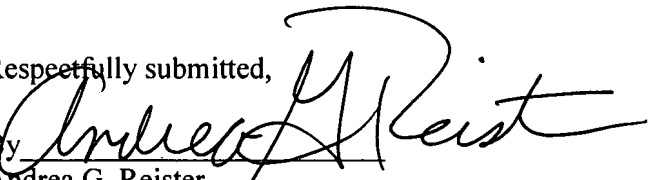
CONCLUSION

Applicants respectfully submit that the foregoing remarks demonstrate that entry of these amendments places the present application in condition for allowance, or alternatively, in better form for consideration on appeal. All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: June 6, 2007

Respectfully submitted,



By
Andrea G. Reister
Registration No.: 36,253
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000
Attorney for Applicant